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PELP1 protein and the estrogen non-genomic signaling pathway

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Estrogen exerts its biological effects through two signal pathways, the genomic and non-genomic pathway, both of which contribute to cell homeostasis. The non-genomic pathway has been suggested to be important in estrogen-induced cardio-, neuron-, and osteoprotection, and confers the ability of the cell to rapidly respond to its environment. The effects of the non-genomic pathway are the regulation of different cellular processes, such as proliferation, survival, apoptosis, and other functions in diverse cell-types. The proline-, glutamic acid-, and leucine-rich protein 1 (PELP1), is now known as a modulator of the estrogen receptors, and is also a novel coregulator of the non-genomic signal pathway with various functions. Therefore, the evaluation of the molecular crosstalk between PELP1 and the non-genomic pathway may lead to the development of functionally selective estrogen receptor modulators which can participate in the multiple functions of estrogen signaling in reproductive tissues and other organs.

estrogen, coregulator, non-genomic pathway, PELP1, cross-talk

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The estrogen 17-β estradiol (E_2) binds to its receptors and cofactors to mediate various hormonal effects which play roles in a wide variety of biological processes in multiple organs including the brain, breast, the cardiovascular system, uterus and bone [1–4]. Estrogen receptors (ER)α and ERβ are the primary members of the estrogen receptor super-family. The mechanisms of ERα and ERβ ligand binding, their dimerization, the association with coactivators or corepressors, and transcriptional regulation through binding to target genes, are well-known and are typically referred to as "genomic" actions. More recently, E_2 and other steroids have been found to have rapid, cytoplasmic actions as well, which are called "non-genomic" actions. The genomic actions are related to maintaining basic cellular functions, including chromatin remodeling and cell cycle progression [5]. The non-genomic actions confer the ability of the cell to dynamically respond to physiological or pathological changes [6].

Recently, PELP1 has been reported to play a role in E_2 signaling in multiple studies. PELP1 acts as an important protein that regulates the effects of estrogen on other signaling pathways. Previous studies showed that PELP1 acts as a scaffolding protein and coregulator of the ER, and participates in both the genomic and non-genomic actions of E_2 signaling [7,8]. Therefore, the evaluation of the interactions between PELP1 and estrogen signaling may lead to the development of functionally selective ER modulators that can separate the beneficial, prodifferentation effects in bone, the cardiovascular system, and the central nervous system, and the detrimental proliferative effects in reproductive tissues and organs.

1 Estrogen signaling pathways

Several studies have shown that the biological effects of E_2 are mediated through two signaling pathways [9]. One is

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referred to as "classical" or "genomic" pathway and is directly related to the ability of E_2 to regulate the expression of genes containing estrogen response-enhancer (ERE) sequences in their promoters [10]. When E_2 binds to the ER, the ligand-activated ER translocates to the nucleus, binds to ERE target genes and stimulates gene transcription. The other pathway is referred to as the "non-classical", "rapid", or "non-genomic" pathway and is directly related to the ability of estrogen signaling to participate in cytoplasmic and membrane-mediated signaling events. The non-genomic pathway intersects with other cell-signaling phosphorylation cascades. The process is insensitive to inhibitors of RNA and protein biosynthesis and, in some cases, can take place in the absence of a nucleus. The non-genomic (transcription-independent) activation of several cytosolic factors (Src, MAPK, PKC and AKT) is how E_2 mediates its biological functions [11].

The idea that estrogen binding to the ER only mediates estrogen-target gene transcription is likely an oversimplification. In fact, recent studies have revealed signaling interactions between the ER and other signal transduction pathways such as "non-genomic pathway". In some studies, the ER non-genomic pathway has been suggested to play a key role in estrogen-induced cardio-, neuro-, and osteoprotection [12].

2 Coregulator of estrogen signaling pathways

The estrogen signaling pathway is highly dependent on and regulated by coregulatory proteins. It is generally accepted that some of the diverse functions of estrogen depends on the differential recruitment of coregulators to the ligand-bound ER complex [13]. Coregulators function by participating in a wide variety of actions including the remodeling and modification of chromatin. Nuclear receptor coregulators function as major regulators of hormone signaling because they have the ability to convey signals to the nuclear receptors and target gene promoters. The direct effects of estrogen signaling and the differential recruitment of coregulators might prime nuclear coactivators or corepressors and the chromatin to set the stage for ER gene transcription, thus defining the outcome of the cellular response to E_2. The most recently identified and studied ER coregulator is the proline-, glutamic acid-, and leucine-rich protein 1 (PELP1).

3 PELP1

3.1 Structure of PELP1

PELP1 was first identified as a 160-kD interacting protein in a GST-SH2 domain pull-down assay. Previous work on PELP1 had shown that this protein contains several motifs and domains that are commonly present in transcriptional coactivators, including nuclear receptor-interacting boxes (LXXLL motifs), a zinc finger, a glutamic acid-rich domain, and two proline-rich domains. A unique feature of PELP1 is its histone-binding region. The proline-rich domains contain PXXP motifs which can interact with signaling proteins containing SH3 domains. LXXLL motifs can interact with nuclear receptors including the estrogen receptor, the androgen receptor, the glucocorticoid receptor, and the progesterone receptor, in a ligand-dependent manner [14]. LXXLL motifs 4 and 5 primarily mediate the binding of PELP1 to the AF2 domain of the ER [8]. Thus PELP1 is also called the coregulator of the ER. Other motifs associate with the histones and can recruit other ER coregulators with histone acetyltransferase activity and bind to the SH2, FHA, SH3, PDZ, and WW domains. Also, PELP1 can interact with important components related to cell cycle progression, including CDK4, cyclin D1, and the retinoblastoma protein (pRb) [15]. Previous studies [11,14] showed that PELP1 could interact with the cytosolic kinases c-Src, phosphatidylinositol-3 kinase (PI3K), and a number of other signaling components, including the epidermal growth factor receptor (EGFR), signal transducer and activator of transcription (STAT), and the hepatocyte growth factor-regulated tyrosine kinase substrate (HRS). PELP1 is also suggested to play a role in modulating local chromatin structure in the vicinity of nuclear receptor promoters with different signaling components.

3.2 Expression of PELP1

PELP1 is expressed in a wide variety of tissues with the highest levels of expression noted in the brain [16], mammary gland, ovaries, and uterus [8,11,17]. Previous studies showed that the function of PELP1 was determined by its expression level and cellular localization [17]. In the rat brain, a study reported high-intensity PELP1 staining colocalized with ERα [15]. It is also highly expressed in the known target organs of estrogen/steroid signaling with the highest levels of expression found during pregnancy [8]. PELP1 is also highly expressed in normal mammary gland [11]. PELP1 contains a central consensus nuclear localization sites and exhibits both nuclear and cytoplasmic localization in a variety of cells in the body [8]. In normal tissues, PELP1 has been shown to reside in both the nucleus and cytoplasm [18]. In hormonally responsive tissues, PELP1 predominantly resides in the nucleus, and localization in the cytoplasm is reduced [19]. Within the nuclear compartment, PELP1 localizes to the nucleoplasm, chromatin, and nuclear matrix [8].

3.3 PELP1 and the estrogen non-genomic signaling pathway

In some E_2 positive tissues, such as bone and endothelial cells, estrogen signaling is transduced predominantly through

the non-genomic pathway which is also called rapid signal pathway [20]. This signaling allows for rapid changes in cell shape and size. The effects occur within minutes, are not blocked by transcriptional and translational inhibitors, and can be activated in many different types of cells by membrane-impermeable ligands. The rapid signaling often initiates at the cell's surface through a mechanism different from that mediated by the ER and its ability to recruit coregulators. Rapid rearrangement of the action cytoskeleton generally depends on the binding of external stimuli to membrane associated receptors, and is mediated via the subsequent rapid action of different protein phosphates and kinases [6], including G-proteins, tyrosine kinase c-Src, caveolin-1, heat shock protein 90, and PELP1. Previous studies have shown that PELP1 plays an important role in estrogen signaling pathways [5,14], especially in non-genomic signaling pathway [21]. PELP1 was found to be an activator of the non-genomic effects of ERα providing a mechanism for coupling ligand binding with the rapid E_2-dependent activation of Src and the downstream MAPK signaling cascade. Src has been identified as a crucial molecule downstream of the ER through its physical interaction with the receptor, and might mediate estrogen's rapid action. The MAPK pathway is involved in the control of many fundamental cellular functions that include differentiation, apoptosis, motility, and metabolism. Previous studies showed that Src/MAPK played a fundamental role in both growth factor and E_2-stimulated cell growth, and regulates both cell proliferation and survival [22]. The ER interacts with Src's SH2 domain, and this complex is stabilized by PELP1. Thus PELP1 mediates a critical step in the activation of c-Src and subsequent MAPK signaling. Moreover, PELP1 also coordinates and promotes complex formation with ERα, and PI3K, which also suggests that PELP1 is an important regulator of cell cycle progression via the PI3K pathway.

In the rapid signal pathway, PELP1 is considered a scaffold protein, and provides functional cross-talk between the growth factor pathways. Cross-talk between growth factor and steroid signaling in the cytoplasm and nucleus may have a profound impact on complex biological processes such as cell growth and proliferation [22,23]. There are four independent lines of evidence of cross-talk between the receptor tyrosine kinase/growth factor and estrogen signaling [24,25]. The first is a G-protein-like transactivation of EGFR proposed to occur via ERα. The second shows a direct interaction of ERα with Shc which acts to couple the activated ER to the Ras/ERK pathway. The third is a G-protein and Src kinase dependent, EGFR independent pathway. Finally there is a cascade involving the interaction of the ER with PELP1 or c-Src, which in turn activates Ras to link the activated ER to the MAPK pathway. Earlier studies also showed that PELP1 promotes growth factor-mediated activation of ER targets genes. PELP1 also participates in the phosphorylation of growth factor which is important in facilitating PELP1 cross-talk with ER signaling [7].

4 Conclusion

PELP1, as a coregulator protein that couples various signaling complexes with the estrogen receptor, plays a key role in the extra nuclear actions of hormone receptors and thus represents a unique ER-coregulator that participates in both the genomic and the non-genomic actions of estrogen signaling. PELP1 is recruited to the promoters of ER target genes, and enhances the transcription of estrogen target genes. In addition, PELP1 plays a role in estrogen-mediated regulation of cell cycle progression and differentiation through a non-genomic pathway. Future studies are needed to address the effect of PELP1 in mediating other effects of estrogen signaling.

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